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Therapeutic Products Directorate
Direction des produits thérapeutiques

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Canadian Adverse Drug Reaction Newsletter

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Dear Health Professional Advisories now available on the Web

The Therapeutic Products Directorate (TPD) and the Biologic and Genetic Therapies Directorate have started posting industry-issued "Dear Health Professional" (DHP) letters on the TPD Web site in July 2000 in addition to the health professional advisories that the Directorates already issued and posted. A new Web page listing entitled "Advisories to Health Professionals" was created on Mar. 23, 2001, and is divided into two sections: one for messages originating from both directorates, and the second for messages prepared in collaboration with both directorates and issued by industry.

DHP letters are an important source of information regarding the post-approval safety and effectiveness of therapeutic products. Recognizing that the public expects this type of information to be made more readily available to all interested parties, we encourage you to share the following Web site address with your colleagues: www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/advhp_e.html

Check the site for full information on the phenylpropanolamine advisory: "Health Canada withdraws drug products containing phenylpropanolamine (PPA) from the market."

2008-02528/

Miconazole–warfarin interaction: increased INR

Recent literature reports have identified the possibility of a serious adverse interaction between vaginal miconazole and warfarin, with potentiation of the anticoagulation effect.[1,2]

The US Food and Drug Administration issued a "Talk Paper" to inform health care professionals that women who take warfarin and use a miconazole vaginal cream or suppository may be at risk of an increased prothrombin time (PT), international normalized ratio (INR) and bleeding tendency.[3]

Hypoprothrombinemia in patients receiving oral anticoagulants in conjunction with oral miconazole has been documented.[4] Small amounts (< 2%) of miconazole are absorbed systemically when the drug is applied vaginally in healthy women of childbearing age.[5] However, recent published case reports of increased INR in 3 women aged 53, 61 and 72 years taking concurrent vaginal miconazole and warfarin, with no identifiable cause for prolonged PT, led the authors to suggest that absorption of vaginal miconazole may be increased in the presence of atrophic vaginal epithelium, potentiating the risk of hypoprothrombinemia.[2]

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) searched its database for cases reporting concurrent use of miconazole (vaginal and topical) and warfarin. As of March 2001, 2 case reports were identified. The first was of a 52-year-old woman taking warfarin who presented to hospital with a hemorrhage of the right kidney after 12 days of using vaginal Monistat. The elevated PT and partial thromboplastin time, recorded on admission, returned to normal after discontinuation of the vaginal Monistat. The second case was of an 80-year-old man using topical miconazole who had a cerebral vascular accident. The causality could not be established because of multiple medical problems and concurrent medications.

Health Canada is taking steps to inform all health care professionals of the potential interactions with intravaginal miconazole and anticoagulants. The sponsors have been requested to update labelling, product monograph and prescribing information for all vaginal products containing miconazole. Because these products are available over the counter, product packaging will include a consumer warning to "Consult a doctor or pharmacist before use if you are taking the blood thinning medicine warfarin, because bleeding or bruising may occur."

Written by: Mano Murty, MD, CCFP, FCFP, Bureau of Licensed Product Assessment

References

1. Thirion DJG, Zanetti LAF. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. *Pharmacotherapy* 2000;20(1):98-9.
2. Lansdorp D, Bressers HPHM, Dekens-Konter JAM, Meyboom RHB. Potentiation of acenocoumarol during vaginal administration of miconazole. *BR J Clin Pharmacol* 1999;47:223-30.
3. US Food and Drug Administration (FDA). *FDA talk paper: FDA updates safety information for miconazole vaginal cream and suppositories.* Rockville (MD): FDA; 2001 Mar 5. Available: www.fda.gov/bbs/topics/ANSWERS/2001/ANS01071.html (accessed 2001 May 18).
4. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interaction of warfarin with drugs and food. *Ann Intern Med* 1994;121:676-83.
5. Daneshmend TK. Systemic absorption of miconazole from the vagina. *J Antimicrob Chemother* 1986;18:507-11.

New health professional/consumer toll-free telephone and fax lines to report ADRs

Effective August 1, 2001, an improvement to facilitate the receipt of drug safety information will be implemented, with the introduction of toll-free telephone and fax access. Health professionals and consumers may use these numbers to report adverse drug reactions (ADRs). Calls will be automatically routed to the appropriate regional or national ADR centre. Reporting access for manufacturers will continue to be through the existing national ADR centre direct lines.

Health professionals/consumers contact us toll free at:
Telephone: 866 234-2345
Fax: 866 678-6789

Rosiglitazone (Avandia): hepatic, cardiac and hematological reactions

Rosiglitazone maleate (Avandia), an oral antidiabetic agent approved for sale in Canada on Mar. 21, 2000, is a member of the thiazolidinedione class of drugs. It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis.[1] Use of rosiglitazone is indicated as monotherapy in patients with type 2 diabetes mellitus not controlled by diet and exercise alone. The drug is also indicated for use in combination with metformin or a sulfonylurea when, in addition to diet and exercise, any one of rosiglitazone, metformin or a sulfonylurea alone do not result in significant improvement of glycemic control. For patients inadequately controlled by a maximum dose of metformin or a sulfonylurea, rosiglitazone should be added to, not substituted for, either metformin or a sulfonylurea.[1]

Troglitazone (Rezulin), another thiazolidinedione, was associated with severe hepatotoxicity and liver failure and was withdrawn from the US market in March 2000 (troglitazone was never marketed in Canada). Although the mechanism of this toxicity remains unknown, it has been suggested that chemically reactive metabolites of troglitazone covalently bind to hepatic proteins, which causes oxidative stress and liver injury.[2] In addition to the potential risk of liver toxicity, thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure.

Upon the market launch of Avandia, the sponsor issued a Dear Health Professional letter[3] to inform about the potential risk of liver toxicity with thiazolidinediones and to provide recommendations for the monitoring of liver function test results and symptoms of heart failure in patients at risk for congestive heart failure. Rosiglitazone is contraindicated in patients with serious hepatic impairment and is not indicated for combination use with insulin.[1] It is also not indicated for use in patients with New York Heart Association class III and IV cardiac status (congestive heart class III and IV) unless the expected benefit is believed to outweigh the potential risk.[3]

The Avandia product monograph includes recommendations for liver enzyme monitoring in all patients:

- baseline liver enzymes and liver enzymes every 2 months for the first 12 months
- liver enzymes periodically thereafter
- more frequent liver monitoring in patients with mild liver enzyme elevations; proceed with caution
- do not initiate therapy in patients with increased baseline liver enzyme levels (alanine aminotransferase [ALT] level > 2.5 times the upper limit of normal)
- if at any time ALT levels increase to > 3 times the upper limit of normal, liver enzymes should be rechecked as soon as possible
- if ALT levels remain > 3 times the upper limit of normal, discontinue Avandia.[1]

Between March 2000 and Feb. 23, 2001, the CADRMP received 166 domestic reports of suspected adverse drug reactions associated with rosiglitazone; 38 were classified as serious[4] — fatal outcomes (3 cases), liver and biliary disorders (10), cardiovascular disorders (20) and hematological disorders (8) — and are summarized here:

Reported fatal outcomes: In the first case of death, a 51-year-old man who was positive for hepatitis B surface antigen, negative for hepatitis B e antigen, positive for hepatitis B e antibody and had relatively normal baseline liver enzyme values (aspartate aminotransferase [AST] 43 [normally < 40] U/L; alkaline phosphatase [AP] 85 [normally < 125] U/L) took rosiglitazone for 6 months and experienced a marked increase in liver enzyme levels (AST 1102 U/L, AP 135 U/L and bilirubin 79 [normally < 25] µmol/L). Rosiglitazone was discontinued, and the man died 1 week later from liver failure. Concurrent medications included metformin, glyburide and amlodipine.

In the second case, a 56-year-old woman with morbid obesity and angina had shortness of breath after using rosiglitazone for 4 months. On admission to hospital an electrocardiogram revealed sinus tachycardia with ventricular premature contractions. The woman died 3 weeks later. The cause of death was listed as probable pulmonary embolism. Concomitant medications included insulin, irbesartan, hydrochlorothiazide, megestrol acetate and diltiazem.

In the third case a 75-year-old man with a history of hypertension took rosiglitazone for an unspecified period of time. He was admitted to hospital because of weakness, suffered a myocardial infarction and subsequently died. Concomitant medications included metoprolol, furosemide and potassium.

Liver and biliary disorders: In all 10 cases of liver and biliary disorders, the reported elevated liver enzymes ranged from less than 2 to more than 3 times the upper limit of normal. The duration of treatment with rosiglitazone ranged from a few weeks to 6 months. At least 3 patients had known hepatic disorders when rosiglitazone treatment was added. In most cases, there was not enough clinical information to allow a meaningful assessment of causality. Baseline liver function test results were not always provided.

Cardiovascular disorders: Of the 20 cases of cardiovascular disorders, 8 were of congestive heart failure or heart failure. In 5 of these cases, onset occurred within 3 days to 6 weeks after the start of rosiglitazone (onset unknown in 3 cases). Patients recovered without sequelae in 3 cases (recovery unknown in 5 cases). Cases of edema without heart failure were also reported.

Hematological disorders: The following hematological reactions were reported in 8 cases: anemia, iron deficiency anemia, decreased hemoglobin concentration, leucopenia, neutropenia, pancytopenia, decreased platelet production, prolonged prothrombin time (PT) and thrombocytopenia. Edema was reported in 3 of the 8 cases. In the case of prolonged PT, warfarin was a concomitant medication.

To minimize the risk of hepatic and cardiovascular adverse events, physicians are advised to adhere to all recommendations listed in the product monograph and to exercise caution when prescribing rosiglitazone to patients with fluid retention, hypertension, mildly elevated liver enzyme levels or underlying cardiac conditions. Also, patients should be instructed to watch for signs of congestive heart failure (shortness of breath, swelling of the lower extremities) and liver problems (nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine or yellowing of the skin).

A second thiazolidinedione drug, pioglitazone (Actos), was approved for use in Canada on Aug. 17, 2000. At product launch, similar warnings with respect to the potential risk of liver toxicity were issued by the sponsor.[5]

Health care professionals are requested to report adverse reactions associated with rosiglitazone and pioglitazone.

Written by: Marielle McMorran, BScPharm, and Duc Vu, PhD,
Bureau of Licensed Product Assessment

References

1. *Avandia TM, rosiglitazone tablets* [product monograph]. Oakville (ON): SmithKline Beecham Pharma; 2000 May 9.
2. Kassahun K, Pearson PG, Tang W, McIntosh I, Leung K, Elmore C, et al. Studies on the metabolism of troglitazone to reactive intermediates in vitro and in vivo. Evidence for novel biotransformation pathways involving quinone methide formation and thiazolidinedione ring scission. *Chem Res Toxicol* 2001;14(1):62-70.
3. *Dear Health Care Professional Letter: Avandia*. Oakville (ON): SmithKline Beecham Pharma; March 2000.
4. *Canadian Adverse Drug Reaction Monitoring Programme guidelines for the voluntary reporting of adverse drug reactions by health professionals*. Ottawa: Therapeutic Products Directorate, Health Canada. Available: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr-guideline_e.html
5. *Dear Healthcare Professional Letter: Actos*. Toronto: Eli Lilly Canada Inc; September 2000.

Adverse drug reaction reporting — 2000: Part 2

The CADRMP received 7361 domestic reports of suspected adverse drug reactions (ADRs) in 2000 that met the minimum criteria of an ADR report (an identifiable reporter, a patient [even if not precisely identified], a suspect drug and a suspect reaction).[1] A steady increase in the reporting of ADRs in Canada over the past 5 years has been noted (Fig. 1). The continued commitment of health care professionals to report ADRs directly affects the success of the CADRMP and is greatly appreciated.

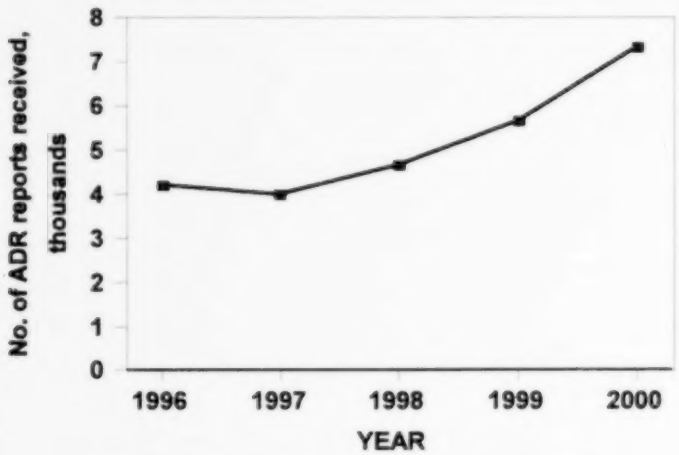

Fig. 1: Number of reports of adverse drug reactions (ADRs) received annually by the Canadian Adverse Drug Reaction Monitoring Program from 1996 to 2000

Of the ADR reports received in 2000, 3343 were classified as serious, and 202 had a fatal outcome. Adverse reactions are suspected associations that reflect the opinion or observation of the individual reporter. A report of a drug–reaction association does not necessarily mean that the reaction was caused by the drug. Assessment of causality, which refers to the association between the reported reactions and the suspected drug product(s), must include an evaluation of other factors such as temporal associations, the possible contribution of concomitant medications or therapies, the underlying disease and the patient's medical history.

A summary of the most frequent drug products involved in the ADR reports is provided in Table 1. The suspect or interacting drugs were grouped according to the American Hospital Formulary Service classification to provide a representation by pharmacologic-therapeutic classification. The CADRMP received 20 or more reports for each active ingredient included in the summary.

Table 1: Suspect products* in reports of adverse drug reactions received in 2000, grouped by AHFS classification

Products (AHFS classification)	% of reports
Central nervous system agents (28:00)	46.5
Anti-infective agents (8:00)	10.3
Cardiovascular drugs (24:00)	8.4
Hormones and synthetic substitutes (68:00)	7.2
Unclassified therapeutic agents (92:00)	7.2
Gastrointestinal drugs (56:00)	5.5
Antineoplastic agents (12:00)	5.0
Blood formulation and coagulation (20:00)	4.9
Diagnostic agents (36:00)	2.5
Skin and mucous membrane agents (84:00)	1.3
Antihistamine drugs (4:00)	1.1

Note: AHFS = American Hospital Formulary Service.
*Active ingredients mentioned in > 20 reports received in 2000.

An ADR report may contain more than one reaction. In total, 18 349 suspected serious and nonserious reactions were reported. All were assessed and coded according to the World Health Organization Adverse Reaction Terminology (WHO-ART). The 10 most frequently occurring types of reactions in the year 2000 are represented by system organ class as follows: body (general disorders) 16.4%, gastrointestinal 11.5%, dermatological 11.2%, central and peripheral nervous system 11.2%, psychiatric 8.7%, respiratory 7.3%, metabolic and nutritional 5%, liver and biliary 3.6%, heart rate and rhythm 3.1%, and urinary 2.6%. Reactions that were reported a minimum of 100 times were identified and then grouped by system organ class.

For additional information or to report an ADR, physicians, pharmacists, other health professionals and consumers are invited to contact the CADRMP.

Written by: Heather Sutcliffe, BScPharm, and Lynn Macdonald, BSP,
Bureau of Licensed Product Assessment

Reference

1. Adverse drug reaction reporting — 2000:Part 1. *Can Adverse Drug React Newsl* 2001;11(2):1. [Also in *CMAJ* 2001;164(7):1038].

COMMUNIQUÉ

The CADRMP wishes to provide feedback and increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the official Canadian product monograph. (Reactions are expressed based on the "preferred term" in the World Health Organization Adverse Reaction Dictionary.)

Orlistat (Xenical) interaction with coumarin derivatives: increased INR
Unexpected increases in the international normalized ratio (INR) were noted after the administration of orlistat to patients taking either warfarin or nicoumalone (Sintrom). Dosage adjustments of the coumarin derivatives or discontinuation of orlistat resulted in the INR returning to normal.

Azithromycin (Zithromax): myocardial infarction
Chest pain was reported after a first dose of azithromycin, and myocardial infarction following the second dose.

DRUGS OF CURRENT INTEREST

The purpose of the Drugs of Current Interest (DOCI) list is to stimulate reporting for a selected group of marketed drugs in order to identify drug safety signals. The maintenance of this list by the CADRMP facilitates regular monitoring and constitutes one element of post-approval assessment activities.

abacavir (Ziagen)
alteplase (Activase rt-PA)
amprenavir (Agenerase)
celecoxib (Celebrex)
clopidogrel (Plavix)
delavirdine (Rescriptor)
efavirenz (Sustiva)
etanercept (Enbrel)
Hypericum perforatum (St. John's Wort)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
melanoma theraccine (Melacine)
meloxicam (Mobicox)
naratriptan (Amerge)
nevirapine (Viramune)
oseltamivir (Tamiflu)
pioglitazone (ACTOS)
ritonavir (Norvir)
rituximab (Rituxan)
rofecoxib (Vioxx)
rosiglitazone (Avandia)
saquinavir (Invirase)
trastuzumab (Herceptin)
zaleplon (Starnoc)
zanamivir (Relenza)
zolmitriptan (Zomig)

If you have observed any suspected ADRs with the drugs in the Communiqué or DOCI list, please report them to the :

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Adverse Reaction Information Unit
Bureau of Licensed Product Assessment
AL: 0201C2, Ottawa, ON K1A 1B9
Tel: (613) 957-0337 Fax: 613 957-0335
cadrmp@hc-sc.gc.ca
or to a participating regional ADR centre.

Consumers and health professionals may contact us free of charge by phone 866 234-2345 or fax 866 678-6789.

The ADR form is available from the *Compendium of Pharmaceuticals and Specialties* and the National and Regional ADR Centres, and at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.pdf

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Queen Elizabeth II Health Sciences Centre
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www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.html

Canada

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are underreported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Directorate monitors and assesses suspected ADRs as a means of continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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